JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 66, NO. 19, 2015

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2015.08.877

EDITORIAL COMMENT

LCZ696 (Sacubitril/Valsartan)

Can We Predict Who Will Benefit?*

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The recent U.S. Food and Drug Administration approval of LCZ696, a combination of sacubitril and valsartan, has generated palpable excitement among heart failure (HF) clinicians (1). Several lines of evidence have pointed to the potential benefits of drugs combining renin-angiotensin-aldosterone system inhibition with enhanced natriuretic peptide activity (2). Neprilysin, a neutral endopeptidase (NEP), degrades endogenous vasoactive peptides, including natriuretic peptides and bradykinin. Neprilysin inhibition results in higher levels of natriuretic peptides, producing vasodilation, sodium excretion, and possible improvement in ventricular remodeling (2). Small trials of LCZ696 in patients with hypertension or HF with preserved ejection fraction demonstrated hemodynamic and neurohormonal effects that were greater than those observed by an angiotensin receptor blocker alone (3).

The multinational, randomized PARADIGM-HF (Prospective Comparison of ARNI and ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial directly compared LCZ696 with enalapril in 8,442 adult patients with New York Heart Association (NYHA) functional class II to IV HF symptoms and left ventricular ejection fractions ≤35% receiving stable doses of beta-blocker and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy (4).

The trial was stopped early for clinical benefit, with a hazard ratio for the primary endpoint of cardiovascular death or HF hospitalization of 0.80 (95% confidence interval: 0.71 to 0.89). Although LCZ696 was more frequently associated with symptomatic hypotension, this did not lead to a higher frequency of drug discontinuation. Renal dysfunction, hyperkalemia, and cough occurred significantly less frequently with LCZ696 than with enalapril. However, a nonsignificant trend for an increase in angioedema with LCZ696 was noted ($p = 0.13$). Packer et al. (5) subsequently demonstrated additional clinical benefit of LCZ696, including a reduced need for intensified HF therapy, inotropic agents, mechanical circulatory support, or heart transplantation. Sustained reductions in myocardial biomarkers (troponin and N-terminal pro-B-type natriuretic peptide [BNP]) were also observed (5).

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In this issue of the *Journal*, Simpson et al. (6) report the results of a post-hoc analysis of PARADIGM-HF to examine the spectrum of risk among trial participants and LCZ696's effect across that spectrum. Although most patients were classified as having mild symptoms (5% in NYHA functional class I and 70% in NYHA functional class II), the correlation between self-reported functional limitation and long-term prognosis in chronic systolic HF is often poor. Thus, NYHA classification encompasses a wide and overlapping range of risks. The investigators calculated baseline prognostic risk using 2 previously validated HF scoring systems: the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) score and the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) score (7,8).

The investigators sought to answer the pivotal question of whether risk based on these clinically validated scores modified LCZ696's treatment. The MAGGIC risk score identified 13 independent

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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predictors of all-cause mortality, including age, male sex, diabetes, systolic blood pressure, left ventricular ejection fraction, obstructive lung disease, renal dysfunction, and the use of neurohormonal antagonists (7). A simple integer score was derived for each patient, with a maximum of 57 points. Similarly, the EMPHASIS-HF risk score included 10 independent risk factors, such as hemoglobin, heart rate, and prior HF hospitalization; the maximal possible score was 12 points (8). Patients were divided into 5 quintiles of MAGGIC risk and 4 quartiles of EMPHASIS-HF risk. The primary composite endpoint of death or HF hospitalization, those 2 components, and all-cause mortality were all analyzed for each risk group and by treatment type using Cox regression modeling.

Not surprisingly, patients in higher quintiles were more likely to have NYHA functional class III or IV symptoms and additional medical comorbidities. When the MAGGIC score was examined as a continuous variable, an increase of 1 point in the overall score was associated with a 6% increased risk for the primary endpoint and a 7% increased risk for cardiovascular death. Importantly, the benefit of LCZ696 over enalapril for the primary endpoint was similar across the entire spectrum of risk. Analysis using the EMPHASIS-HF score produced similar findings. Whether analyzed as continuous or categorical variables, LCZ696 provided the greatest absolute benefit in those at highest risk. The investigators conclude that, within the overall PARADIGM-HF population, there was a substantial subset with much to gain from angiotensin receptor and neprilysin inhibition over a relatively short period of time (6).

Although these findings are impressive, various limitations must be considered. First and foremost, this was a non-pre-specified post-hoc analysis with the inherent limitations and potential for unrecognized bias. In addition, trial patients were generally younger (mean age 64 years), had better preserved systolic blood pressures, and had less renal dysfunction than many "real-life" HF populations. Furthermore, neither prognostic risk score included natriuretic peptide biomarkers, which are powerful predictors of outcome. Also, the MAGGIC score was developed to estimate all-cause mortality, not to stratify patients for other outcomes such as HF hospitalizations. Unlike angiotensin-converting enzyme inhibitors, LCZ696 has not yet been demonstrated to produce favorable effects on ventricular remodeling. The safety of introducing LCZ696 during hospitalization for acute decompensated HF has yet to be systematically assessed. Finally, it is increasingly common that serum biomarkers such as BNP, N-terminal pro-BNP, and ST2 are used in clinical practice to guide pharmacological intensification. Whether these biomarkers can be used to monitor treatment efficacy remains unknown.

Assays for quantitative measurement of soluble serum neprilysin (sNEP) levels and NEP catalytic activity have recently become available. sNEP levels have been shown to predict short- and long-term prognosis in acute decompensated HF, independent of N-terminal pro-BNP (9). Importantly, there appears to be substantial biologic "crosstalk" between circulating natriuretic peptides and NEP activity. Vodovar et al. (10) demonstrated in patients with acute HF that elevated immunoreactive BNP (BNP plus N-terminal pro-BNP) levels >916 pg/ml significantly inhibit NEP's catalytic activity. This new finding raises concern about whether patients with chronic advanced HF, typically characterized by very high BNP levels, may have an attenuated clinical response to an exogenous NEP inhibitor such as LCZ696 because of suppression of NEP catalytic activity (11). Future studies should examine whether either sNEP levels or NEP activity may help clinicians identify those patients most likely to respond to LCZ696 and whether serial measurement of these novel biomarkers may help optimize dosing (11).

Finally, 2 safety concerns that were not fully addressed in this study are undergoing evaluation. Angioedema, which was first observed with the angiotensin-converting enzyme and neprilysin inhibitor omapatrilat, was expected to be eliminated using the angiotensin receptor blocker and neprilysin inhibitor. However, angioedema was more frequently reported in the LCZ696 cohort (19 cases) than the enalapril cohort (10 cases). The exact frequency of this adverse event remains to be quantified. Additionally, beta-amyloid is also a recognized substrate for neprilysin; its inhibition may block the breakdown of this key peptide that has been implicated in the pathogenesis and progression of Alzheimer's disease. Cognitive functional changes will require serial assessment during long-term treatment, particularly in elderly patients.

The investigators have provided valuable information suggesting that this new class of pharmacological inhibitor can produce major benefits in a wide spectrum of patients with systolic HF. For the practicing clinician, several unanswered question remain. First, should circulating sNEP levels and/or NEP catalytic activity be routinely measured and used to guide LCZ696 therapeutic decisions? Second, which patients in stable condition should be switched from their current renin-angiotensin-aldosterone system inhibitors to LCZ696? Unlike clinical practice,

every trial patient underwent a controlled run-in period during which tolerability was carefully assessed. Despite the exclusion of numerous potential study candidates, symptomatic hypotension remained greater in the LCZ696 group. This suggests that patients with borderline blood pressures or those tolerating lower than recommended doses of vasodilator therapy may encounter difficulties with LCZ696. The MAGGIC and EMPHASIS-HF scores help predict prognosis but do not aid in optimizing patient selection. It would appear that patients with mild to moderate HF and adequate systolic blood pressures on maintenance renin-angiotensin-aldosterone system inhibitor therapy would be most suited for transition to this new agent. Establishing the optimal regimen for conversion and up-titration of LCZ696 remains a short-term challenge.

Nonetheless, this is a good "problem" to have, as a new class of agents with major benefits is on the horizon and should substantially improve our approach to managing chronic systolic HF.

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KEY WORDS neprilysn inhibition, sacubitril/valsartan